We claim:

1. A method of alleviating pain in a subject, comprising

administering to said subject a pharmaceutical composition comprising an effective amount of an α-adrenergic agonist and a pharmaceutical composition comprising an effective amount of a selective α-2A antagonist.

2. The method of claim 1, wherein said pain is neuropathic pain.

3. The method of claim 2, wherein said pain results from diabetic neuropathy.

4. The method of claim 1, wherein said pain is visceral pain.

5. The method of claim 1, wherein said pain is post-operative pain.

6. The method of claim 1, wherein said pain results from cancer or cancer treatment.

7. The method of claim 1, wherein said pain is inflammatory pain.

8. The method of claim 7, wherein said pain is arthritic pain.

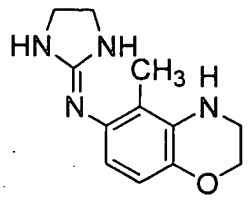
9. The method of claim 7, wherein said pain is irritable bowel syndrome pain.

10. The method of claim 1, wherein said pain is headache pain.

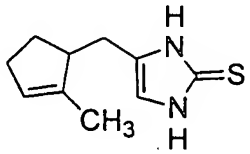
11. The method of claim 1, wherein said α-adrenergic agonist is a pan-α-2 agonist.

12. The method of claim 11, wherein said pan-α-2 agonist is a pan-α-1 pan-α-2 agonist.

13. The method of claim 1, wherein said α-adrenergic agonist is a compound selected from the group consisting of clonidine, brimonidine, tizanidine, dexemedetomidine, norepinephrine, a compound represented by the formula



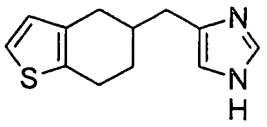
[FORMULA 1], a compound represented by the formula



[FORMULA 2], and all pharmaceutically acceptable salts, esters, amides, sterioisomers and racemic mixtures thereof.

14. The method of claim 1, 11, 12 or 13, wherein said selective α-2A antagonist is a 4-imidazole or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

15. The method of claim 14, wherein said selective α-2A antagonist is a compound represented by the formula



[FORMULA 13] or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

16. The method of claim 1, wherein said selective α-2A antagonist is BRL 48962 or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

17. The method of claim 1, wherein said selective α-2A antagonist is peripherally limited.

18. The method of claim 1, wherein said α-adrenergic agonist and said selective α-2A antagonist each is administered peripherally.

19. The method of claim 1 or claim 18, wherein said α-adrenergic agonist is administered orally.

20. The method of claim 1 or claim 18, wherein said selective α-2A antagonist is administered orally.

21. The method of claim 1 or claim 18, wherein said α-adrenergic agonist is administered through a subcutaneous minipump.

22. The method of claim 1 or claim 18, wherein said selective α-2A antagonist is administered through a subcutaneous minipump.

23. The method of claim 1, wherein said α-adrenergic agonist and said selective α-2A antagonist each is administered repeatedly or continuously over a period of at least three days.

24. The method of claim 23, wherein pain alleviation continues in the absence of significant α-adrenergic agonist levels in said subject.

25. An analgesic composition, comprising an α-adrenergic agonist with minimal α-2A agonist activity, said agonist having the ability to produce peripheral analgesia without concomitant sedation.

26. The analgesic composition of claim 25, wherein said peripheral analgesia is sufficient to reduce pain by at least 50% without concomitant sedation.

27. The analgesic composition of claim 26, wherein at least a 10-fold greater dose is required to produce a 20% reduction in motor or muscular activity than the dose required to reduce pain by at least 50%.

28. The analgesic composition of claim 27, wherein at least a 100-fold greater dose is required to produce a 20% reduction in motor or muscular activity than the dose required to reduce pain by at least 50%.

29. The analgesic composition of claim 28, wherein at least a 1000-fold greater dose is required to produce a 20% reduction in motor or muscular activity than the dose required to reduce pain by at least 50%.

30. The analgesic composition of claim 25 or claim 26, further having a substantial absence of hypotensive effects.

31. The analgesic composition of claim 25 or claim 26, wherein said agonist is not a thiourea or a derivative thereof.

32. The analgesic composition of claim 25 or claim 26, wherein said agonist is not a thiourea or 4-imidazole or a derivative thereof.

33. A method of alleviating pain in a subject, comprising peripherally administering to said subject a pharmaceutical composition comprising an effective amount of an α-adrenergic agonist with minimal α-2A agonist activity,

thereby producing peripheral analgesia without concomitant sedation.

34. The method of claim 33, wherein said peripheral analgesia is sufficient to reduce pain by at least 50% without concomitant sedation.

35. The method of claim 33 or claim 34, wherein said peripheral analgesia occurs in the substantial absence of hypotensive effects.

36. The method of claim 33 or claim 34, wherein said α-adrenergic agonist with minimal α-2A agonist activity is not a thiourea or a derivative thereof.

37. The method of claim 33 or claim 34, wherein said α-adrenergic agonist with minimal α-2A agonist activity is not a thiourea or 4-imidazole or a derivative thereof.

38. The method of claim 33, wherein said pain is neuropathic pain.

39. The method of claim 38, wherein said pain results from diabetic neuropathy.

40. The method of claim 33, wherein said pain is visceral pain.

41. The method of claim 33, wherein said pain is post-operative pain.

42. The method of claim 33, wherein said pain results from cancer or cancer treatment.

43. The method of claim 33, wherein said pain is inflammatory pain.

44. The method of claim 43, wherein said pain is arthritic pain.

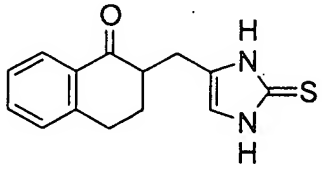
45. The method of claim 43, wherein said pain is irritable bowel syndrome pain.

46. The method of claim 33, wherein said pain is headache pain.

47. The method of claim 33, wherein said α-adrenergic agonist with minimal α-2A agonist activity is an α-2B agonist with minimal α-2A agonist activity.

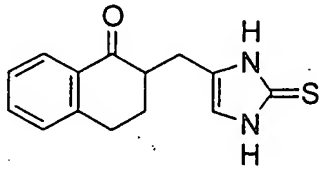
48. The method of claim 47, wherein said α-2B agonist with minimal α-2A agonist activity is a thione.

49. The method of claim 48, wherein said α-2B agonist with minimal α-2A agonist activity is a compound represented by the formula



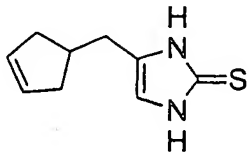
[FORMULA 3] or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

50. The method of claim 49, wherein said α-2B agonist with minimal α-2A agonist activity is the (-) enantiomer of a compound represented by the formula



[FORMULA 3] or a pharmaceutically acceptable salt or ester thereof.

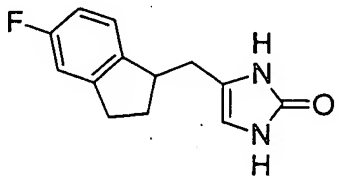
51. The method of claim 48, wherein said α-2B agonist with minimal α-2A agonist activity is a compound represented by the formula



[FORMULA 11] or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

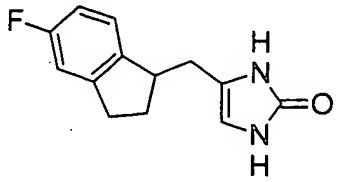
52. The method of claim 47, wherein said α-2B agonist with minimal α-2A agonist activity is an imidazolone.

53. The method of claim 52, wherein said α-2B agonist with minimal α-2A agonist activity is a compound represented by the formula



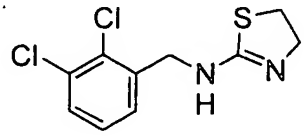
[FORMULA 4] or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

54. The method of claim 53, wherein said α-2B agonist with minimal α-2A agonist activity is the (+) enantiomer of a compound represented by the formula

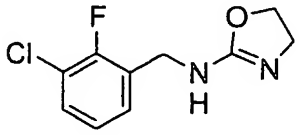


[FORMULA 4] or a pharmaceutically acceptable salt or ester thereof.

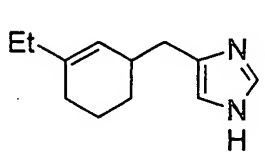
55. The method of claim 47, wherein said α-2B agonist with minimal α-2A agonist activity is a compound represented by a formula selected from the group consisting of



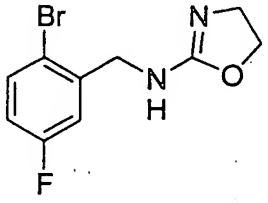
[FORMULA 5],



[FORMULA 6],



[FORMULA 9],



[FORMULA 14],

and all pharmaceutically acceptable salts, esters, amides, sterioisomers and racemic mixtures thereof.

56. The method of claim 33, wherein said α-adrenergic agonist with minimal α-2A agonist activity is administered orally.

57. The method of claim 33, wherein said α-adrenergic agonist with minimal α-2A agonist activity is administered through a subcutaneous minipump.

58. A method of screening for effective agents that produce peripheral analgesia without concomitant sedation, comprising the steps of:

(a) contacting an α-2A receptor with an α-adrenergic agonist having analgesic activity; and

(b) determining whether said agonist has α-2A agonist activity,

wherein the absence of α-2A agonist activity indicates that said α-adrenergic agonist having analgesic activity is an effective agent that produces peripheral analgesia without concomitant sedation.

59. A method of screening for effective agents that produce peripheral analgesia without concomitant sedation, comprising the steps of:

(a) contacting an α-2A receptor with an agent;

(b) determining whether said agent has α-2A agonist activity;

(c) contacting an α-2B receptor with said agent; and

(d) determining whether said agent has α-2B agonist activity,

wherein the absence of α-2A agonist activity and the presence of α-2B agonist activity indicate that said agent is an effective agent that produces peripheral analgesia without concomitant sedation.

60. A method of screening for effective agents that produce peripheral analgesia without concomitant sedation, comprising the steps of:

(a) peripherally administering an α-adrenergic agonist to a control animal having at least wild type levels of α-2A receptor activity;

(b) assaying for analgesia in said control animal;

(c) peripherally administering to a corresponding animal having reduced levels of α-2A receptor expression or activity an amount of said α-adrenergic agonist similar or greater than the amount administered to said control animal; and

(d) assaying for analgesia in said corresponding animal having reduced levels of α-2A receptor expression or activity,

wherein the absence of analgesia in said control animal and the presence of analgesia in said corresponding animal having reduced levels of α-2A receptor expression or activity indicate that said α-adrenergic agonist has excessive α-2A agonist activity; and

wherein the presence of analgesia in said control animal and the presence of analgesia in said corresponding animal having reduced levels of α-2A receptor expression or activity indicate that said α-adrenergic agonist is an effective agent that produces peripheral analgesia without concomitant sedation.

61. The method of claim 60, wherein said control animal is wild type at both α-2A receptor loci.

62. The method of claim 61, wherein said control animal is a wild type animal.

63. The method of claim 62, wherein said wild type animal is a wild type mouse.

64. The method of claim 60 or 63, wherein said corresponding animal has a homozygous point mutation at the α-2A receptor locus.

65. The method of claim 64, wherein said corresponding animal has a point mutation within the α-2A receptor coding sequence.

66. The method of claim 65, wherein said point mutation occurs at a residue analogous to Asp79.

67. The method of claim 66, wherein said point mutation is an Asp79 to Asn mutation.

68. The method of claim 60 or 63, wherein said corresponding animal has a homozygous α-2A knockout mutation.

69. The method of claim 60 or 63, wherein, in steps (b) and (d), analgesia is assayed following sulprostone sensitization.

70. The method of claim 60, further comprising:

(e) peripherally administering said α-adrenergic agonist to a corresponding animal having reduced levels of α-2B receptor expression or activity; and

(f) assaying for analgesia in said corresponding animal having reduced levels of α-2B receptor expression or activity,

wherein the absence of analgesia in said control animal and the presence of analgesia in said corresponding animal having reduced levels of α-2A receptor expression or activity indicate that said α-adrenergic agonist has excessive α-2A agonist activity; and

wherein the presence of analgesia in said control animal, the presence of analgesia in said corresponding animal having reduced levels of α-2A receptor expression or activity and the absence of analgesia in said corresponding animal having reduced levels of α-2B receptor expression or activity indicate that said α-adrenergic agonist is an effective agent that produces peripheral analgesia without concomitant sedation.

71. A method of screening for effective agents that produce peripheral analgesia without concomitant sedation, comprising the steps of:

(a) peripherally administering an α-adrenergic agonist to a control animal having at least wild type levels of α-2B receptor activity;

(b) assaying for analgesia in said control animal;

(c) peripherally administering said α-adrenergic agonist to a corresponding animal having reduced levels of α-2B receptor expression or activity; and

(d) assaying for analgesia in said corresponding animal having reduced levels of α-2B receptor expression or activity,

wherein the presence of analgesia in said control animal and the absence of analgesia in said corresponding animal having reduced levels of α-2B receptor expression or activity indicate that said α-adrenergic agonist is an effective agent that produces peripheral analgesia without concomitant sedation.

72. The method of claim 71, wherein said control animal is wild type at both α-2B receptor loci.

73. The method of claim 72, wherein said control animal is a wild type animal.

74. The method of claim 73, wherein said wild type animal is a wild type mouse.

75. The method of claim 71, wherein said corresponding animal has a heterozygous α-2B knockout mutation.

76. The method of claim 71, wherein said corresponding animal has a homozygous α-2B knockout mutation.

77. The method of claim 71 or 74, wherein, in steps (b) and (d), analgesia is assayed following sulprostone sensitization.

78. A method for the long-term relief of chronic pain in a subject, comprising activating in said subject an analgesic α-adrenergic receptor in the absence of α-2A receptor activation over a period of at least three days,

such that relief of chronic pain is maintained in the absence of continued activation of said receptor.

79. The method of claim 78, comprising administering to said subject a pharmaceutical composition comprising an effective amount of an α-adrenergic agonist with minimal α-2A agonist activity over a period of at least three days,

such that relief of chronic pain is maintained in the absence of significant agonist levels in said subject.

80. The method of claim 78, comprising administering to said subject a pharmaceutical composition comprising an effective amount of an α-adrenergic agonist and a pharmaceutical composition comprising an effective amount of a selective α-2A antagonist over a period of at least three days,

such that relief of chronic pain is maintained in the absence of significant agonist levels in said subject.

81. The method of claim 79 or 80, wherein relief of chronic pain is maintained for at least three weeks in the absence of significant agonist levels in said subject.

82. The method of claim 78, wherein said pain is neuropathic pain.

83. The method of claim 82, wherein said pain results from diabetic neuropathy.

84. The method of claim 78, wherein said pain is visceral pain.

85. The method of claim 78, wherein said pain is post-operative pain.

86. The method of claim 78, wherein said pain results from cancer or cancer treatment.

87. The method of claim 78, wherein said pain is inflammatory pain.

88. The method of claim 87, wherein said pain is arthritic pain.

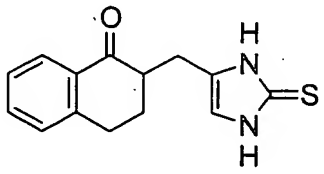
89. The method of claim 87, wherein said pain is irritable bowel syndrome pain.

90. The method of claim 78, wherein said pain is headache pain.

91. The method of claim 79, wherein said α-adrenergic agonist with minimal α-2A agonist activity is an α-2B agonist with minimal α-2A agonist activity.

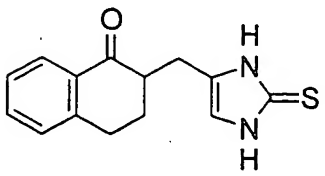
92. The method of claim 91, wherein said α-2B agonist with minimal α-2A agonist activity is a thione.

93. The method of claim 92, wherein said α-2B agonist with minimal α-2A agonist activity is a compound represented by the formula



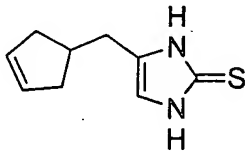
[FORMULA 3] or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

94. The method of claim 93, wherein said α-2B agonist with minimal α-2A agonist activity is the (-) enantiomer of a compound represented by the formula



[FORMULA 3] or a pharmaceutically acceptable salt or ester thereof.

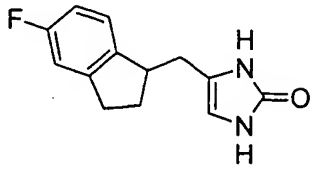
95. The method of claim 92, wherein said α-2B agonist with minimal α-2A agonist activity is a compound represented by the formula



[FORMULA 11] or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

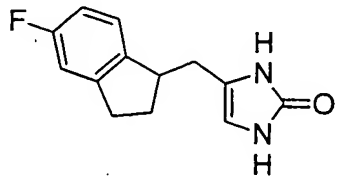
96. The method of claim 91, wherein said α-2B agonist with minimal α-2A agonist activity is an imidazolone.

97. The method of claim 96, wherein said α-2B agonist with minimal α-2A agonist activity is a compound represented by the formula



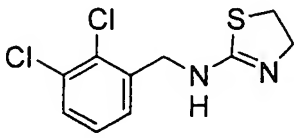
[FORMULA 4] or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

98. The method of claim 97, wherein said α-2B agonist with minimal α-2A agonist activity is the (+) enantiomer of a compound represented by the formula

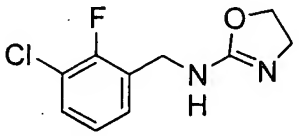


[FORMULA 4] or a pharmaceutically acceptable salt or ester thereof.

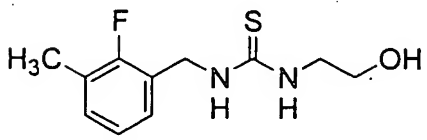
99. The method of claim 91, wherein said α-2B agonist with minimal α-2A agonist activity is a compound represented by a formula selected from the group consisting of



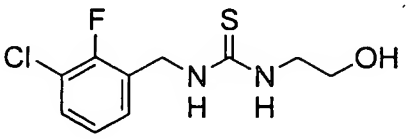
[FORMULA 5],



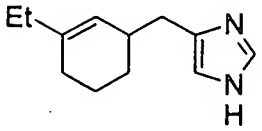
[FORMULA 6],



[FORMULA 7],



[FORMULA 8],



[FORMULA 9], and all pharmaceutically acceptable salts, esters, amides, sterioisomers and racemic mixtures thereof.

100. The method of claim 79, wherein said α-adrenergic agonist with minimal α-2A agonist activity is administered peripherally.

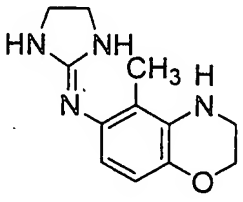
101. The method of claim 100, wherein said α-adrenergic agonist with minimal α-2A agonist activity is administered orally.

102. The method of claim 100, wherein said α-adrenergic agonist with minimal α-2A agonist activity is administered through a subcutaneous minipump.

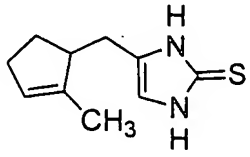
103. The method of claim 80, wherein said α-adrenergic agonist is a pan-α-2 agonist.

104. The method of claim 103, wherein said pan-α-2 agonist is a pan-α-1 pan-α-2 agonist.

105. The method of claim 80, wherein said α-adrenergic agonist is a compound selected from the group consisting of clonidine, brimonidine, tizanidine, dexemedetomidine, norepinephrine, a compound represented by the formula



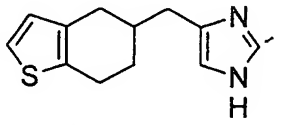
[FORMULA 1], a compound represented by the formula



[FORMULA 2], and all pharmaceutically acceptable salts, esters, amides, sterioisomers and racemic mixtures thereof.

106. The method of claim 80, 103, 104 or 105, wherein said selective α-2A antagonist is a 4-imidazole or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

107. The method of claim 106, wherein said selective α-2A antagonist is a compound represented by the formula



[FORMULA 13] or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

108. The method of claim 80, 103, 104 or 105, wherein said selective α-2A antagonist is BRL 48962 or a pharmaceutically acceptable salt, ester, amide, sterioisomer or racemic mixture thereof.

109. The method of claim 80, 103, 104 or 105, wherein said selective α-2A antagonist is peripherally limited.

110. The method of claim 80, wherein said α-adrenergic agonist and said selective α-2A antagonist each is administered peripherally.

111. The method of claim 80 or claim 110, wherein said α-adrenergic agonist is administered orally.

112. The method of claim 80 or claim 110, wherein said α-2A antagonist is administered orally.

113. The method of claim 80 or claim 110, wherein said α-adrenergic agonist is administered through a subcutaneous minipump.

114. The method of claim 80 or claim 110, wherein said selective α-2A antagonist is administered through a subcutaneous minipump.